

The University of Chicago

A CASE OF BIOLOGICAL PERIODICITY

A PART OF A DISSERTATION SUBMITTED
TO THE FACULTY OF THE DIVISION OF THE
PHYSICAL SCIENCES IN CANDIDACY FOR THE
DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSICS

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ALVIN M. WEINBERG

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INTRODUCTION

Examples of periodicities in biology have been known for a long time; in fact, some of the most obvious and fundamental biological phenomena (such as reproduction, the heart beat, etc.) are periodic in character. Inasmuch as periodical changes in the cell are found to be connected with the rhythm of cellular division, a study of such periodicities is of particular interest for a general theory of cellular multiplication and growth. N. Rashevsky has shown that on the basis of a certain postulated mechanism, the possibility of periodic variation of concentration of metabolizing substances in a cell could be demonstrated. However, in his discussion Rashevsky has confined himself to the case in which the diffusion coefficients inside and outside the cell are infinite.

In this paper we propose to examine the more general case in which the external diffusion coefficient is infinite while the internal coefficient is finite. We shall consider, with Rashevsky, a case in which two substances are being metabolized in a spherical cell. We shall suppose the reactions involving the two substances to be so linked that the rate of production of one substance per unit volume is proportional to a linear combination of the concentrations of both substances. Thus if c_1 and c_2 are the concentrations of the two substances, then

$$\text{rate of production of } c_1 = A_{11}c_1 + A_{12}c_2$$

$$\text{rate of production of } c_2 = A_{21}c_1 + A_{22}c_2.$$

Depending on the signs of the coefficients, several cases can be distinguished. For example, if all the A 's are negative, the two substances are being consumed; if A_{11} , A_{22} are negative and A_{12} , A_{21} are positive, the rate of production of one substance is proportional to its own concentration while its rate of consumption is proportional to the concentration of the other.

The setting up of the partial differential equations which govern the variations in concentration follows immediately from previous work. Assuming the internal coefficients of diffusion constant, we have for the amount of each material flowing into a small volume element $\Delta x \Delta y \Delta z$

$$D_i \nabla^2 c_i \Delta x \Delta y \Delta z.$$

If the change in concentration per second per unit volume is $\partial c_i / \partial t$, then to have a material balance inside the cell

$$\left. \begin{aligned} \frac{\partial c_1}{\partial t} &= D_1 \nabla^2 c_1 + A_{11}c_1 + A_{12}c_2 \\ \frac{\partial c_2}{\partial t} &= D_2 \nabla^2 c_2 + A_{21}c_1 + A_{22}c_2 \end{aligned} \right\}. \quad (1)$$

In the general case of finite external D a similar set of equations with all the A 's = 0 would hold outside the cell. However, we shall assume infinite external D 's for simplicity; this implies that the concentrations are constant ($=c_{0i}$) everywhere outside the cell. Such an assumption corresponds physically to turbulence in the medium surrounding the cell.

If we consider our cell to be spherical with center at the origin, the c_i become functions of r alone and equations (1) become

$$\left. \begin{aligned} \dot{c}_1 &= D_1 c_1'' + \frac{2}{r} D_1 c_1' + A_{11} c_1 + A_{12} c_2 \\ \dot{c}_2 &= D_2 c_2'' + \frac{2}{r} D_2 c_2' + A_{21} c_1 + A_{22} c_2 \end{aligned} \right\} \quad (2)$$

where dots represent time derivatives and primes derivatives with respect to r . As boundary conditions we take

1. At center of cell, concentrations remain finite:

$$\text{i.e.,} \quad c_1 \Big|_{r=0}, \quad c_2 \Big|_{r=0} \quad \text{finite.}$$

2. At surface of cell $r=r_0$

$$\begin{aligned} D_1 c_1' \Big|_{r_0} &= h_1 (c_{01} - c_1) \Big|_{r_0} \\ D_2 c_2' \Big|_{r_0} &= h_2 (c_{02} - c_2) \Big|_{r_0} \end{aligned}$$

where h_1 and h_2 are the permeabilities of the cell membrane for the two substances. Equations (2) can be simplified by the usual substitution $u_i = c_i r$ to

$$\left. \begin{aligned} D_1 u_1'' &= \dot{u}_1 - A_{11} u_1 - A_{12} u_2 \\ D_2 u_2'' &= \dot{u}_2 - A_{21} u_1 - A_{22} u_2 \end{aligned} \right\} \quad (3)$$

with boundary conditions

$$\begin{aligned} 1.) \quad & u_1(0) = u_2(0) = 0 \\ 2.) \quad & \left. \begin{aligned} u_1' \Big|_{r_0} &= \frac{D_1 - h_1 r_0}{D_1 r_0} u_1 \Big|_{r_0} + \frac{h_1 r_0 c_{01}}{D_1} \\ u_2' \Big|_{r_0} &= \frac{D_2 - h_2 r_0}{D_2 r_0} u_2 \Big|_{r_0} + \frac{h_2 r_0 c_{02}}{D_2} \end{aligned} \right\} \end{aligned} \quad (4)$$

Solution of Equations

A. Time independent equation.

The solution of (3) will in general consist of a linear combination of a function

involving the time and a function independent of time. Thus we may assume

$$u_i = w_i(r, t) + y_i(r) \quad (5)$$

where y_i are the solutions of

$$\left. \begin{aligned} D_1 y_1'' &= -A_{11} y_1 - A_{12} y_2 \\ D_2 y_2'' &= -A_{21} y_1 - A_{22} y_2 \end{aligned} \right\} \quad (6)$$

with suitable boundary conditions, and w_i are the solutions of (3) with u replaced by w . The boundary conditions are easily found by putting (5) into (4) and equating time dependent and independent parts. Thus

$$\left. \begin{aligned} 1.) \quad y_1 \Big|_{r=0} &= y_2 \Big|_{r=0} = 0 \\ 2.) \quad y_1' \Big|_{r_0} &= \frac{D_1 - h_1 r_0}{D_1 r_0} y_1 \Big|_{r_0} + \frac{h_1 r_0 c_{01}}{D_1} \\ y_2' \Big|_{r_0} &= \frac{D_2 - h_2 r_0}{D_2 r_0} y_2 \Big|_{r_0} + \frac{h_2 r_0 c_{02}}{D_2} \end{aligned} \right\} \quad (7)$$

and

$$\left. \begin{aligned} 1.) \quad w_1 \Big|_{r=0} &= w_2 \Big|_{r=0} = 0 \\ 2.) \quad w_1' \Big|_{r_0} &= \frac{D_1 - h_1 r_0}{D_1 r_0} w_1 \Big|_{r_0} \\ w_2' \Big|_{r_0} &= \frac{D_2 - h_2 r_0}{D_2 r_0} w_2 \Big|_{r_0} \end{aligned} \right\} \quad (8)$$

The system (6) is linear and homogeneous, and its boundary conditions (7) are non-homogeneous. Its solution, which is immediate, is

$$\left. \begin{aligned} y_1 &= F \sin \mu_1 r + G \sin \mu_2 r \\ y_2 &= \xi(\mu_1) F \sin \mu_1 r + \xi(\mu_2) G \sin \mu_2 r \end{aligned} \right\} \quad (9)$$

where μ_1 and μ_2 are roots (assumed distinct) of

$$\left| \begin{array}{cc} A_{11} - D_1 \mu^2 & A_{12} \\ A_{21} & A_{22} - D_2 \mu^2 \end{array} \right| = 0, \quad (10)$$

$$\xi(\mu) = \frac{D_1 \mu^2 - A_{11}}{A_{12}} = \frac{A_{21}}{D_2 \mu^2 - A_{22}},$$

and

$$\left. \begin{aligned} F &= \frac{\xi(\mu_2)\alpha_{22}h_1r_0D_2c_{01} - \alpha_{12}h_2r_0D_1c_{02}}{D_1D_2\{\xi(\mu_2)\alpha_{11}\alpha_{22} - \xi(\mu_1)\alpha_{12}\alpha_{21}\}} \\ G &= \frac{\alpha_{11}h_2r_0D_1c_{02} - \xi(\mu_1)\alpha_{21}h_1r_0D_2c_{01}}{D_1D_2\{\xi(\mu_2)\alpha_{11}\alpha_{22} - \xi(\mu_1)\alpha_{12}\alpha_{21}\}}, \end{aligned} \right\} \quad (11)$$

where

$$\alpha_{ij} = \mu_j \cos \mu_j r_0 - \frac{D_i - h_i r_0}{D_i r_0} \sin \mu_j r_0.$$

B. Time dependent equation:

It proves to be convenient in discussing the time dependent equation to change the units of t so that $D_1 = p$, $D_2 = 1/p$, $p > 1$ if $D_1 > D_2$. The new parameter p will satisfy these conditions if we put

$$t_{\text{new}} = \frac{D_1}{p} t_{\text{old}}, \quad p^2 = \frac{D_1}{D_2}.$$

In these units our time dependent equations are

$$\left. \begin{aligned} \frac{1}{p} \dot{w}_1 - w_1'' &= a_{11}w_1 + a_{12}w_2 \\ p \dot{w}_2 - w_2'' &= a_{21}w_1 + a_{22}w_2 \end{aligned} \right\} \quad (12)$$

where $a_{11} = A_{11}/D_1$, $a_{21} = A_{21}/D_2$, etc.

Our problem now is to determine solutions of (12) which satisfy the homogeneous boundary conditions (8). First we can show that no undamped periodic solutions of (12) exist if a_{12} and a_{21} have the same sign. To this end we assume a solution of (12) of the form

$$\left. \begin{aligned} w_1 &= \sqrt{\pm a_{12}} [\psi_1(r) - \psi_2(r)] e^{\lambda t} \\ w_2 &= \sqrt{\pm a_{21}} [\psi_1(r) + \psi_2(r)] e^{\lambda t} \end{aligned} \right\} \quad (13)$$

(where $-$ sign is used if a_{12} , $a_{21} < 0$), and substitute into (12). The resulting equations and boundary conditions are

$$\left. \begin{aligned} \psi_1'' &= M_{11}\psi_1 + M_{12}\psi_2 + \lambda N_{11}\psi_1 + \lambda N_{12}\psi_2 \\ \psi_2'' &= M_{21}\psi_1 + M_{22}\psi_2 + \lambda N_{21}\psi_1 + \lambda N_{22}\psi_2 \end{aligned} \right\} \quad (14)$$

and

$$\left. \begin{aligned} 1.) \quad \psi_1 \Big|_{r=0} &= \psi_2 \Big|_{r=0} = 0 \\ 2.) \quad \psi_1' \Big|_{r_0} + k_1 \psi_1 \Big|_{r_0} + k_2 \psi_2 \Big|_{r_0} &= 0 \\ \psi_2' \Big|_{r_0} + k_2 \psi_1 \Big|_{r_0} + k_1 \psi_2 \Big|_{r_0} &= 0 \end{aligned} \right\}. \quad (15)$$

The constants M_{ij} , N_{ij} , and k_1 are real functions of the a 's, h 's and p ; for our purposes it is sufficient to note that

$$\begin{aligned}M_{12} &= M_{21}, \\N_{11} &= N_{22} = 1/2(p + 1/p), \\N_{12} &= N_{21} = 1/2(p - 1/p).\end{aligned}$$

These relations insure that system (14) is "self-adjoint" (Hilbert, 1921)—hence all the "characteristic numbers" λ are real. Since the λ 's occur in the exponential in (13), if they are all real no periodicities are possible.

The transformation (13) is not real in case a_{12} and a_{21} have opposite signs and so this method cannot then be used to prove anything about the λ 's. However, if we make the further simplifying assumption that $h_1/D_1 = h_2/D_2$ we can solve (12) completely.*

First we make the substitution in (12) and (8):

$$\left. \begin{aligned}w_1 &= \theta e^{lt} z_1(r, t) \\w_2 &= e^{lt} z_2(r, t)\end{aligned} \right\} \quad (16)$$

where

$$\theta^2 = -\frac{a_{12}}{a_{21}}, \quad \frac{a_{12}}{\theta} = -\theta a_{21} = b,$$

and l and a are chosen so that

$$\left. \begin{aligned}2l &= pa_{11} + \frac{1}{p} a_{22} \\2a &= pa_{11} - \frac{1}{p} a_{22}\end{aligned} \right\}. \quad (17)$$

The resulting equation is

$$\left. \begin{aligned}\frac{1}{p} \dot{z}_1 - z_1'' &= \frac{1}{p} a z_1 + b z_2 \\p \dot{z}_2 - z_2'' &= -b z_1 - p a z_2\end{aligned} \right\} \quad (18)$$

and the boundary conditions (8) are still satisfied by z_i . We assume that z_i is the product of an exponential time and an exponential space factor so that $\dot{z}_i = \lambda z_i$, $z_i'' = \kappa^2 z_i$. Putting these expressions into (18) we find

$$\left. \begin{aligned}[\kappa^2 - (\lambda - a)/p] z_1 + b z_2 &= 0 \\-b z_1 + [\kappa^2 - p(\lambda + a)] z_2 &= 0\end{aligned} \right\}. \quad (19)$$

For a non-trivial solution we must have $z_2 = \xi z_1 \neq 0$; thus

$$\left. \begin{aligned}\kappa^2 - (\lambda - a)/p &= -b\xi \\ \kappa^2 - p(\lambda + a) &= b/\xi\end{aligned} \right\}. \quad (20)$$

* That in many cases such an assumption is reasonable is shown by J. Reiner (1938).

This pair of equations, when solved for λ and κ^2 , yield

$$\begin{aligned}\lambda &= -[A(p + 1/p) + B(\xi + 1/\xi)], \\ \kappa^2 &= -[2A + B(p\xi + 1/p\xi)],\end{aligned}\quad (21)$$

where

$$A = \frac{a}{p - 1/p}, \quad B = \frac{b}{p - 1/p}.$$

The value of λ is unchanged if we substitute $\xi' = 1/\xi$; on the other hand, if $\xi \neq \pm 1$, we get two different values for κ , κ_1 and κ_2 , corresponding to ξ and $1/\xi$. This means that two linearly independent solutions of (18) corresponding to the same λ are

$$\left. \begin{aligned} z_{11} &= e^{\lambda t} e^{\kappa_1 r} \\ z_{21} &= \xi e^{\lambda t} e^{\kappa_1 r} \end{aligned} \right\} \quad (22)$$

and

$$\left. \begin{aligned} z_{12} &= e^{\lambda t} e^{\kappa_2 r} \\ z_{22} &= \frac{1}{\xi} e^{\lambda t} e^{\kappa_2 r} \end{aligned} \right\} \quad (23)$$

where

$$\left. \begin{aligned} \kappa_1^2 &= -[2A + B(p\xi + 1/p\xi)] \\ \kappa_2^2 &= -[2A + B(p/\xi + \xi/p)] \end{aligned} \right\}. \quad (24)$$

The general solution of (18) may now be written

$$\left. \begin{aligned} z_1 &= (\alpha e^{\kappa_1 r} + \beta e^{-\kappa_1 r} + \gamma e^{\kappa_2 r} + \delta e^{-\kappa_2 r}) e^{\lambda t} \\ z_2 &= \left(\xi \alpha e^{\kappa_1 r} + \xi \beta e^{-\kappa_1 r} + \frac{\gamma}{\xi} e^{\kappa_2 r} + \frac{\delta}{\xi} e^{-\kappa_2 r} \right) e^{\lambda t} \end{aligned} \right\}. \quad (25)$$

The ξ and λ are still undetermined; they are to be found by applying the boundary conditions (8) which we shall rewrite for convenience:

$$\left. \begin{aligned} 1.) \quad z_1 \Big|_{r=0} &= z_2 \Big|_{r=0} = 0 \\ 2.) \quad z_1' \Big|_{r_0} + s_1 z_1 \Big|_{r_0} &= 0 \\ z_2' \Big|_{r_0} + s_2 z_2 \Big|_{r_0} &= 0 \end{aligned} \right\}. \quad (26)$$

In these equations s_i is an abbreviation for $(h_i r_0 - D_i)/D_i r_0$; $s_1 = s_2$ by the assumption $h_1/D_1 = h_2/D_2$. Putting (25) into (26) we obtain the following system:

$$\left. \begin{array}{l} \alpha + \qquad \qquad \beta + \qquad \qquad \gamma + \qquad \qquad \delta = 0 \\ \xi\alpha + \qquad \qquad \xi\beta + \qquad \frac{1}{\xi}\gamma + \qquad \frac{1}{\xi}\delta = 0 \\ (\kappa_1 + s_1)e^{\kappa_1 r_0}\alpha + (s_1 - \kappa_1)e^{-\kappa_1 r_0}\beta + (\kappa_2 + s_1)e^{\kappa_2 r_0}\gamma + (s_1 - \kappa_2)e^{-\kappa_2 r_0}\delta = 0 \\ \xi(\kappa_1 + s_1)e^{\kappa_1 r_0}\alpha + \xi(s_1 - \kappa_1)e^{-\kappa_1 r_0}\beta + (\kappa_2 + s_1)e^{\kappa_2 r_0}\gamma/\xi + (s_1 - \kappa_2)e^{-\kappa_2 r_0}\delta/\xi = 0 \end{array} \right\} . \quad (27)$$

These equations are homogeneous in α, β, γ , and δ . They will have a non-trivial solution if and only if the determinant of coefficients vanishes. This condition may be written

$$(\xi - 1/\xi)^4(\kappa_1 \cosh \kappa_1 r_0 + s_1 \sinh \kappa_1 r_0)(\kappa_2 \cosh \kappa_2 r_0 + s_1 \sinh \kappa_2 r_0) = 0, \quad (28)$$

as can be shown by simple algebra. The values of λ (κ_i are functions of λ) which satisfy this equation are the required characteristic values. Excluding the case $\xi = \pm 1$ (since, as mentioned before, this case does not give enough linearly independent solutions), we find

$$\frac{\kappa_1}{s_1} = -\tanh \kappa_1 r_0, \quad (29)$$

or

$$\frac{\kappa_2}{s_1} = -\tanh \kappa_2 r_0. \quad (30)$$

Equations (29) and (30) are of standard form (Byerly, 1894) and can be solved graphically for κ_1 and κ_2 . It is convenient to this end to put $\kappa = im$ where m is real; then

$$m = s_1 \tan m r_0 \quad (30A)$$

in either case. The characteristic values λ fall into two classes: those for which $\kappa_1 = im$ and those for which $\kappa_2 = im$. There is no a priori reason to expect these two classes of λ to be the same. To determine the λ 's of class 1, we substitute $\kappa_1 = im$ in (24):

$$m^2 = 2A + B(p\xi + 1/p\xi)$$

or

$$p\xi = \frac{m^2 - 2A}{2B} \pm \sqrt{(m^2 - 2A)^2/4B^2 - 1}$$

and

$$\frac{1}{p\xi} = \frac{m^2 - 2A}{2B} \mp \sqrt{(m^2 - 2A)^2/4B^2 - 1}.$$

Thus

$$B(\xi + 1/\xi) = (p + 1/p)(m^2 - 2A)/2 \pm (p - 1/p)\sqrt{(m^2/2 - A)^2 - B^2}$$

and substituting this expression into (21) we find

$$\lambda = -m^2(p + 1/p)/2 \mp (p - 1/p)\sqrt{(m^2/2 - A)^2 - B^2}. \quad (31)$$

In the same way by substituting $\kappa_2 = im$ in (24) we find the λ 's of class 2 to be given also by expression (31), so that the two classes of characteristic λ 's fall together. It may be remarked that if $s_1 \neq s_2$ so that equation (28) does not break into two factors, this degeneracy is removed.

Since there are infinitely many characteristic functions (corresponding to the infinity of λ 's) we can expect that the complete solution of (2) will be an infinite series of the same general sort that enters in the solution of the vibrating string problem. The validity of the so-called expansion theorem, by virtue of which any initial concentration can be expressed as an infinite sum of characteristic functions, can be demonstrated, but the proof is somewhat lengthy, and so will be omitted. The complete solution of (2) thus turns out to be

$$\left. \begin{aligned} c_1(r, t) &= \frac{1}{r} \left\{ \sum_{i=1}^{\infty} E_{1i} \sin m_i r e^{(\lambda_i + l)t} + F \sin \mu_1 r + G \sin \mu_2 r \right\} \\ c_2(r, t) &= \frac{1}{r} \left\{ \sum_{i=1}^{\infty} E_{2i} \sin m_i r e^{(\lambda_i + l)t} + \xi(\mu_1) F \sin \mu_1 r + \xi(\mu_2) G \sin \mu_2 r \right\} \end{aligned} \right\}, \quad (32)$$

where

$$\begin{aligned} E_{ji} &= \{ [2(m_i r_0)^2 (D/h)^2 + (r_0 - D/h)^2] / [r_0(m_i r_0)(D/h)^2 + r_0^2 - (D/h)^2] \} \\ &\times \int_0^{r_0} [rc_j(r, 0) - y_j(r)] \sin m_i r dr, \end{aligned}$$

and expressions for all other constants have already been given.

C. Transition to the limit:

Rashevsky has shown that in the limiting case of infinite diffusion coefficients the concentrations are exponential functions of the time of the form $e^{\Lambda t}$, where

$$\begin{aligned} \Lambda &= -\frac{1}{2} \left\{ \left(\frac{3h_1}{r_0} - A_{11} + \frac{3h_2}{r_0} - A_{22} \right) \right. \\ &\quad \left. \pm \sqrt{\left(\frac{3h_1}{r_0} - A_{11} + \frac{3h_2}{r_0} - A_{22} \right)^2 - 4 \left[\left(\frac{3h_1}{r_0} - A_{11} \right) \left(\frac{3h_2}{r_0} - A_{22} \right) - A_{12} A_{21} \right]} \right\}. \end{aligned}$$

As a check on the correctness of our results we shall show that for large D the concentrations given in (32) obey an exponential law with this same expression for Λ .

By (30A)

$$\frac{D_1}{D_1 - r_0 h_1} m_i r_0 = \tan m_i r_0; \quad (33)$$

hence as D_1 (and $D_2 = h_2 D_1 / h_1$) approaches ∞ , $D_1 / (D_1 - r_0 h_1)$ approaches 1 and

$m_i r_0 = \tan m_i r_0$. This implies that the first non-zero root, m_1 , of (30A) becomes small as D becomes large. Expanding $\tan m_1 r_0$ in Taylor's series,

$$D_1(m_1 r_0) = (D_1 - r_0 h) \tan m_1 r_0 = (D_1 - r_0 h) [m_1 r_0 + (m_1 r_0)^3/3 + \dots]$$

or since $D_1 \gg r_0 h$, we can neglect terms involving $r_0 h$ multiplied by the third or higher power of $m_1 r_0$ and so

$$D_1(m_1 r_0)^3/3 \simeq h_1 m_1 r_0^2,$$

or

$$m_1^2 \simeq 3h_1/D_1 r_0.$$

If this expression for m_1^2 is put into (31) and the result simplified, it is found that

$$\begin{aligned} \lambda_1 &= -\frac{1}{2} \{ (3h_1 + 3h_2)/r_0 \\ &\quad \pm \sqrt{(-A_{11} - A_{22} + [3h_1 + 3h_2]/r_0)^2 - 4[(A_{11} - 3h_1/r_0)(A_{22} - 3h_2/r_0) - A_{12}A_{21}]} \} \\ &= -\frac{1}{2} \{ (3h_1 + 3h_2)/r_0 \pm \sqrt{R} \}, \end{aligned}$$

where R stands for the expression under the radical. Since $l = \frac{1}{2}(A_{11} + A_{22})$, the first harmonic in (32) has its period determined by

$$\lambda_1 + l = -\frac{1}{2} \{ -A_{11} - A_{22} + (3h_1 + 3h_2)/r_0 \pm \sqrt{R} \}$$

which is the same as Λ . The space dependent part of the first harmonic in (32) reduces to a constant, since the coefficients E_{ji} are constants and $(\sin m_1 r)/r$ approaches m_1 as m_1 becomes small.

As far as the higher harmonics in (32) are concerned, we simply note that from (33) m_i ($i > 1$) is finite and so Dm_i^2 becomes infinite with D . Also, examination of the normalizing factor $1/N_i$ in the expressions for E_{ji} in case the D 's are large, shows that

$$\frac{1}{N_i} = 2(h/D)^2 [(m_i r_0)^2 + 1]/r_0 (h/D)^2 [(m_i r_0)^2 - 1]$$

which is always finite. Since λ_i contains a term $-m_i^2(h_1 D_1 + h_2 D_2/h_1)$, as D becomes large, this term becomes large, and the exponential $e^{\lambda_i t}$ becomes negligible.

Discussion of results

In the old units the exponential factor in the first harmonic can be written $e^{(\lambda_1 + l)t}$, where

$$\begin{aligned} \lambda_1 + l &= \frac{1}{2}(A_{11} + A_{22}) - [m_1^2(D_1 + D_2)/2] \\ &\quad \mp (D_1 - D_2) \sqrt{[m_1^2/2 - (A_{11} - A_{22})/2(D_1 - D_2)]^2 - |A_{12}A_{21}|/(D_1 - D_2)^2}. \end{aligned} \quad (34)$$

For an undamped, periodic first harmonic, $(\lambda_1 + l)$ must be a pure imaginary. This will be so provided the constants A_{ij} and D_i satisfy

$$A_{11} + A_{22} - m_1^2(D_1 + D_2) = 0, \quad (35)$$

and

$$|A_{12}A_{21}|/(D_1 - D_2)^2 > [m_1^2/2 - (A_{11} - A_{22})/2(D_1 - D_2)]^2. \quad (36)$$

Since the m_i increases monotonically, if the first harmonic is undamped all higher harmonics will be damped, and so, for any given set of constants, at most, one undamped harmonic can occur.

The condition (35) which must be satisfied for undamped periodicity is a very stringent one, and we would expect it to hold only in rare cases. Ordinarily the oscillations will be damped, and only relation (36) will be satisfied. This means that $A_{12}A_{21}$ and $(A_{11} - A_{22})^2$ are of the same order at least as $D^2m_1^4$. We can reasonably assume both $A_{12}A_{21}$ and $(A_{11} - A_{22})^2$ to be of approximately the same order as the square of any one reaction constant, say A_{ij} . Also, since $0 < m_1 < \pi/2r_0$, for ordinary values of h , r_0 , and D we would expect $m \sim 1/r_0$. Relation (36) thus implies

$$A_{ij} \geq D/r_0;$$

that is for small cells (r_0 small), A_{ij} (the rates of reaction) must be large and this, from (34), means short periods. This result is biologically plausible: periodic processes (such as reproduction) in bacteria (small size) have short periods; similarly, high rates of metabolism are rather the rule in bacteria.

The dependence of period on temperature can be found roughly by assuming, as a first approximation, that the reaction constants satisfy the Arrhenius relation, $A_{ij} = k_{ij}e^{-u/RT}$, and that the D_i and h_i are sensibly constant. The A_{ij} increases with T and from the previous remarks this implies a decrease in period with increase in temperature. This result is in accordance with the generally observed increase of biological frequencies with temperature.*

Numerical examples

The order of magnitude of the periods obtained when biologically plausible values of the constants are used can be indicated by the following two examples:

Case I:

If

$$\begin{aligned} D_1 &= 6 \times 10^{-7} \text{ cm.}^2 \text{ sec.}^{-1} & D_2 &= 3 \times 10^{-7} \text{ cm.}^2 \text{ sec.}^{-1} \\ h_1 &= 2 \times 10^{-4} \text{ cm. sec.}^{-1} & h_2 &= 10^{-4} \text{ cm. sec.}^{-1} \\ A_{11} &= \pi^2/4 \times 10^{-1} \text{ sec.}^{-1} & A_{12} &= -4 \times 10^{-1} \text{ sec.}^{-1} \\ A_{21} &= 4 \times 10^{-1} \text{ sec.}^{-1} & A_{22} &= 0 \\ r_0 &= 3 \times 10^{-3} \text{ cm.} \end{aligned}$$

then, from (30A),

$$m_1 = \pi/6 \times 10^3 \text{ cm.}^{-1},$$

* An interesting discussion of temperature characteristics for Alpha brain waves has been given by Hoagland, Cameron and Rubin (1937), in which the increase in frequency with temperature is pointed out. The mechanism suggested in this paper is of a "relaxation oscillation" type, which is different from our postulated mechanism.

and from (34),

$$\lambda_1 + l \doteq \mp (4/10)i,$$

and the period of the first harmonic is

$$P = 2\pi / |\lambda_1 + l| \doteq 15 \text{ seconds.}$$

All higher harmonics are damped; for example the real part of $\lambda_2 + l$ is about -2 sec^{-1} and so the second harmonic falls to $1/e$ th of its original value in $1/2$ second. The third and higher harmonics are damped even more.

Case II:

If

$$\begin{aligned} D_1 &= 10^{-6} \text{ cm.}^2 \text{ sec.}^{-1} & D_2 &= \frac{1}{2} \times 10^{-6} \text{ cm.}^2 \text{ sec.}^{-1} \\ h_1 &= 10^{-4} \text{ cm. sec.}^{-1} & h_2 &= \frac{1}{2} \times 10^{-4} \text{ cm. sec.}^{-1} \\ A_{11} &= \frac{3}{8}\pi^2 \times 10^{-2} \text{ sec.}^{-1} & A_{12} &= \pi/2 \times 10^{-2} \text{ sec.}^{-1} \\ A_{21} &= \pi \times 10^{-2} \text{ sec.}^{-1} & A_{22} &= 0 \\ r_0 &= 10^{-2} \text{ cm.} \end{aligned}$$

then

$$m_1 = \pi/2 \times 10^2 \text{ cm.}^{-1},$$

and

$$\lambda_1 + l \doteq \pi/2 \times 10^{-2}i,$$

so that the period of the first harmonic is

$$P \doteq 400 \text{ seconds.}$$

In this case the second harmonic falls to $1/e$ th of its original value in $1/3$ second.

Comparison of the periods in these two cases shows that the larger cell has the longer period as was remarked before.

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SUMMARY

The possibility of periodic concentration changes in metabolizing cells is shown to exist in the case of an idealized spherical cell in which two coupled reactions involving two substances are going on. The periods of these oscillations are calculated, using plausible biological values for the cell constants (diffusion coefficient, permeability, etc.), and are found to be of the order of a few minutes.

A possible correlation of these theoretical results with the generally observed increase in frequencies with increased temperature or decreased cell size is suggested.

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